AD_____

Award Number: W81XWH-10-1-1043

TITLE: FES-Rowing versus Zoledronic Acid to Improve Bone Health in SCI

PRINCIPAL INVESTIGATOR: Leslie R. Morse, DO

CONTRACTING ORGANIZATION: Spaulding Rehabilitation Hospital
Boston, MA 02114

REPORT DATE: OCTOBER, 2012

TYPE OF REPORT: Revised Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2012	Revised Annual Report	30 September 2011- 29 September 2012

4. TITLE AND SUBTITLE
FES-Rowing v. Zoledronic Acid to Improve Bone Health in SCI:

5a. CONTRACT NUMBER
W81XWH-10-1-1043

5b. GRANT NUMBER
W81XWH-10-1-1043

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Leslie R. Morse, DO

E-Mail: lmorse4@partners.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Spaulding Rehabilitation Hospital, Boston, MA 02114

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

There is no established treatment to prevent bone loss or to induce new bone formation following SCI, although the risk is high in this population of osteoporosis-related bone fracture. This study aims to learn if the severe osteoporosis in lower extremities caused by spinal cord injuries can be slowed or reversed with a combination of an exercise that simulates weight-bearing and a bisphosphonate medication. 70 Individuals with T3-12 spinal cord injuries will be enrolled in a 12-month regime of adapted FES-rowing. Our preliminary study findings demonstrated this exercise led to new bone formation and improved bone micro architecture in the lower extremities of people with SCI. Half of the subjects also receive a bisphosphonate medication known to slow bone loss, but not stimulate bone renewal.

Participant recruitment began in late February, 2011, and is continuing. We have enrolled 47 subjects who are at various stages of the study protocol. At this point, there are no significant findings to report.

15. SUBJECT TERMS
SCI, Osteoporosis, FES-rowing, zoledronic acid, exercise, bone health

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	10	USAMRMC

Table of Contents

Introduction

Serious spinal cord injury (SCI) causes osteoporosis in the lower extremities, significantly increasing the risk of bone fracture in this population. However, there currently is no established treatment to prevent bone loss or to induce new bone formation following SCI.

The goal of this clinical trial -- *FES-Rowing versus Zoledronic Acid to Improve Bone Health in SCI* – is to develop an evidence-based therapeutic protocol to address a prevalent and significant health issue in this population. A second aim is to better understand the bone biology and bone health of people with serious SCI.

The trial calls for 70 subjects with SCI to participate in a 12-month adapted FES-rowing program. Half of the subjects also receive a one-time infusion of zoledronic acid, a bisphosphonate used to treat osteoporosis, usually in older women.

We demonstrated in our preliminary studies that functional electrical stimulation (FES) rowing stimulates bone formation and improved bone micro-architecture in the lower extremity. Bisphosphonate medications slow bone loss but do not stimulate new bone formation. Therefore, combination treatment with a bone-building stimulus (FES-rowing) and a medication that stops bone loss (bisphosphonate) may result in greater improvements in bone compared to either agent alone. We are using DXA and CT bone scans to compare changes in bone density and health pre- and post-rowing and bisphosphonate treatment. The results of this study should provide a better understanding of possible therapies to maintain bone strength among people with SCI.

Body

We received final Department of Defense approval to begin active subject recruiting in February, 2011. In the past year we have focused on recruitment and enrollment, row training, and data collection. To date, we have enrolled 47 subjects and have another 30 strong potential candidates. Among the enrolled subjects, 14 have finished strength training and begun the 12-months rowing program and 5 have received the zoledronic acid infusion. We have scheduled final testing for the first 2 subjects who have completed 1 year of rowing and expect 7 more to complete the study over the next 3-6 months.

Statement of Work, Task 1: Study preparation, human subjects approval, finalize instruments, procedures, protocols; research coordinators

This task was completed during the first year of the study.

Statement of Work, Task 2: Recruitment and screening

We continue to send recruitment mailings to current and former spinal cord injury patients of Spaulding Rehabilitation Hospital, the Veterans Administration Boston Healthcare, and Massachusetts General Hospital. Those mailings also included members of the Greater Boston Chapter of the National Spinal Cord Injury Association (GBC-NSCIA).

Besides the mailings and follow-up phone calls, we have used flyers, posters, and digital displays for recruitment. We have placed notices with Massachusetts General Hospital's targeted email service of notifying potential candidates (RSVP). The Paralyzed Veterans of America-Massachusetts Chapter, at our request, published in its newsletter, *Cord Word,* an article on SCI and bone health written by Dr. Morse, study PI, as well as publishing our flyer; both were also posted on the organization's website. The NSCIA-Greater Boston Chapter also posted notice of the study on its website.

In addition, we have sought recruiting assistance from:

- Easter Seals of Massachusetts,
- the Massachusetts Rehabilitation Commission,
- the Massachusetts Recreation Department/Accessible Rec Division,
- adapted sports programs in the Greater Boston area,
- independent living organizations,
- visiting nurses and other home healthcare associations,
- rehabilitation centers,
- college and university disability offices,
- Boston Medical Center's SCI Program, and
- physicians who specialize in people with disabilities.

Their assistance has ranged from posting flyers to informing their staff of the study, to contacting their members, clients, or patients directly or via Facebook, websites, or e-mail.

Spaulding Rehabilitation Hospital's inpatient and out-patient clinicians have offered great support by bringing the trial to the attention of appropriate patients.

We are confident we will meet our enrollment goal of 70 subjects.

Statement of Work, Task 3: Enrollment, randomization, baseline testing

We have enrolled 47 individuals. 25 of the 47 consented participants were randomized to the drug treatment arm of the study.

Baseline bone density scanning, blood draws (renal function, vitamin D levels, calcium levels, bone turnover markers), and distribution of calcium and vitamin D supplements have been carried out successfully at the VA Boston Healthcare-Jamaica Plain Campus. Among participants who have been tested as of October, 2012, 19 were found to have a vitamin D deficiency (<than 30ng/ml) and were treated with supplemental vitamin D. No subject has been excluded from participation based on screening blood work (ie renal function has been adequate in all subjects).

Statement of Work, Task 4: 6-month measurements

14 subjects have had their midpoint data collection – bone density scans, as well as blood draws to check vitamin D, renal function, and future analysis of bone turnover markers.

Statement of Work, Task 5: FES-row training

14 subjects have transitioned from strength-training to active rowing. We anticipate 25 more will enter the rowing phase in the next 2-3 months.

Statement of Work, Task 6: Zoledronic acid infusion

Five subjects have received the zoledronic acid infusion at the VA Boston Healthcare-Jamaica Plain Campus. The nurse practitioner who administered the infusion makes follow-up phone calls within 24 hours to check on how the subject is feeling. 20 additional subjects have been randomized to the treatment arm of the study and will receive the infusion once strength training is complete.

Statement of Work, Task 7: 18-month measurements

We have scheduled final testing for the first 2 subjects who have completed 1 year of rowing and expect 7 more to complete the study over the next 3-6 months. We expect 15 additional subjects to complete the study over the next 12 months.

Statement of Work, Task 8: Data analysis

We are currently analyzing cross-sectional data collected for the first 47 subjects enrolled.

Key Research Accomplishments

This is an intervention study focused on bone outcomes. Given that a cycle of bone remodeling is 3 months, our main outcomes are at 1 year after initiation of training. A period of strength training is required before the initiation of the 1 year period and this can vary from 2 weeks to several months. As this report reflects activities through the end of the second year, and we had a substantial delay in startup pending Department of Defense IRB approval, no key research accomplishments would be expected until years 3 and 4. Below we detail our preliminary findings to date. Biomarker analysis is done in batches to limit variability.

Preliminary Findings to Date:
As of October 2012, we have enrolled 47 participants, 25 to the zoledronic acid infusion arm and 22 to the exercise only arm. Of those enrolled there are 45 males and 2 females. There are 5 motor incomplete injuries and 42 motor complete injures. The mean age was 39.5 (21.1-65.1) and the mean years post injury was 10.2 (0.08-37.5). A total of 39 have had baseline blood work, 37 have had their baseline DXA scan and 27 have had their baseline CT.

Subject Characteristics:

Variable	ZA Infusion and Exercise Arm n=25	Exercise Only Arm n=22
Demographics		
Age (Mean ± SD) [years]	39.8 ± 12.9	39.2 ± 11.7
Age (Range) [years]	21.5-63.5	21.1-65.1
White %	18 (72.0%)	17 (77.3%)
Male %	25 (100%)	20 (90.9%)
Duration of SCI (Mean ± SD) [years]	11.8 ± 13.0	11.4 ± 8.6
Duration of SCI (Range) [years]	0.30-37.8	2.8-32.3
Motor Complete Injury %	23 (92.0%)	19 (86.4%)
BMI [Mean ± SD] (kg/m^2)	24.3 ± 5.0	27.5 ± 4.5
Vitamin D (Mean ± SD)	33.4 ± 9.7	24.6 ± 9.5
• Deficient <30 ng/ml	8 (40.0%)	11 (64.7%)
• Sufficient ≥30 ng/ml	12 (60.0%)	6 (35.3%)
Smoking History		
• Current smoker	2 (10.0%)	2 (11.1%)
• Former smoker	6 (30.0%)	3 (16.7%)
• Never smoker	12 (60.0%)	13 (72.2%)

Baseline Bone Density/Incidence of Osteoporosis at the Hip:

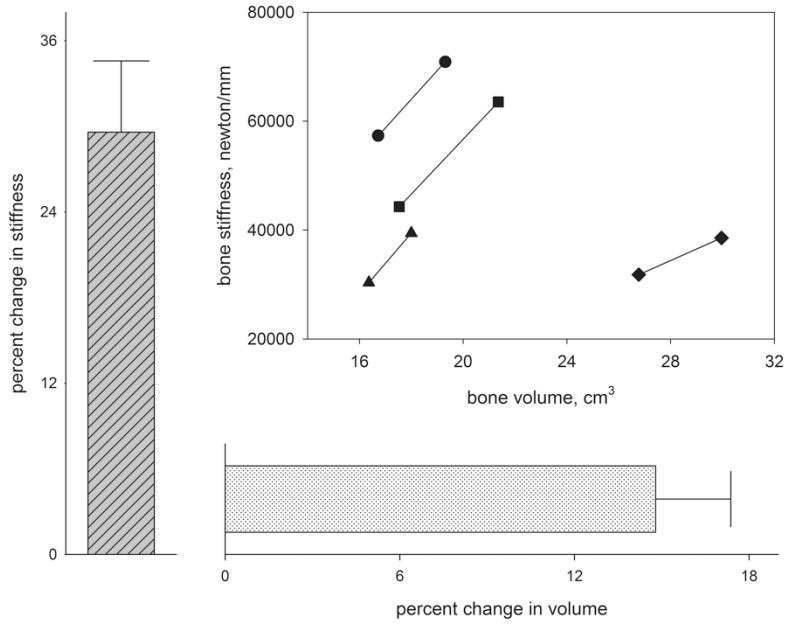
We scanned at traditional bone density sites (femoral neck, total hip and radius) as well as SCI specific skeletal sites (distal femur and proximal tibia) as these are the sites were fractures are most common within the SCI population. For subjects age 50 or older, T-score was used to classify hip bone density (total hip and femoral neck) according to the World Health Organization (WHO) definitions of normal (T-score $\geq$-1), osteopenia (T-score <-1 and >-2.5) and osteoporosis (T-score $\leq$-2.5). For subjects under the age of 50, Z-score was used to classify hip bone density as normal (Z-score >-2) or as lower than expected for age and sex (Z-

score ≤ -2). A total of 38.3% of the participants were classified as having osteoporosis/BMD lower than expected for age. Four participants had no hip data available for analysis due to contracture and 7 are pending dxa scans.

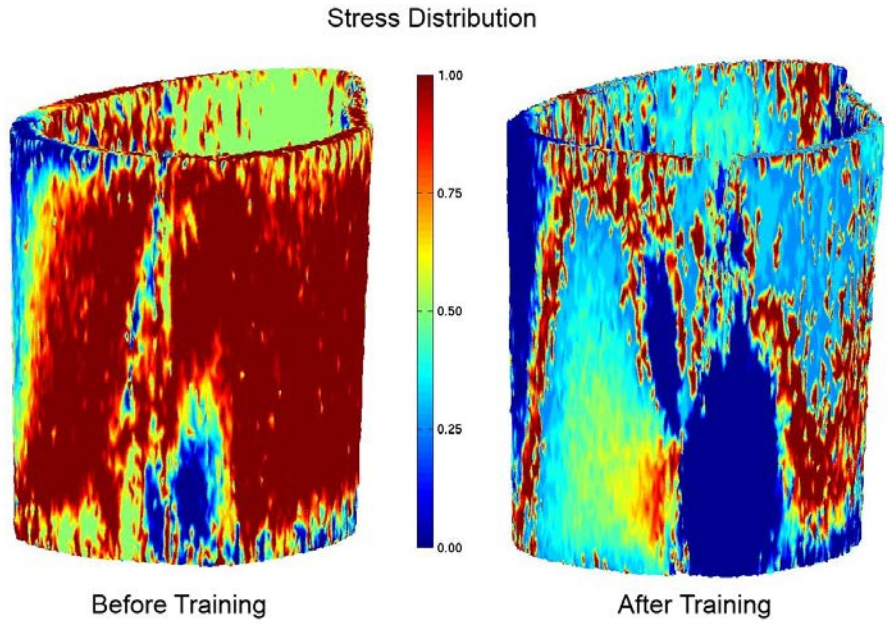
Bone Mineral Density (Mean ± SD) (Range) [g/cm^2]		
SCI Specific Sites		
• Distal femur	0.765 ± 0.24	0.714 ± 0.22
• Proximal tibia	0.805 ± 0.32	0.705 ± 0.20
Traditional Sites		
• Femoral Neck	0.854 ± 0.20	0.796 ± 0.20
• Total Hip	0.846 ± 0.23	0.777 ± 0.22
• Radius	0.993 ± 0.08	0.994 ± 0.09
Osteoporosis status		
• Normal	9 (36.0%)	6 (27.3%)
• Osteopenia	2 (8.0%)	1 (4.5%)
• Osteoporosis/BMD lower than expected for age	9 (36.0%)	9 (40.9%)
• No hip BMD available	5 (20.0%)	6 (27.3%)

Baseline Vitamin D Status:
Of those tested, 19 were found to have a vitamin D deficiency (<than 30ng/ml) and were treated with supplemental vitamin D. After completing the round of repletion, 13 had corrected vitamin D levels greater than 30 ng/ml. After repletion, everyone takes a standard dose of vitamin D and calcium. The average vitamin D value was 29.1 ng/ml (std=10.49, range 7-46.1).

Improvements in Bone Stiffness: 4 subjects have completed rowing (1 ZA infusion and 3 rowing only). We performed finite element analysis to calculate changes in bone volume and bone stiffness in response to rowing. A 3D model of the proximal tibia was created from the volumetric CT images. A 10 mm section of the proximal tibia was segmented from the surrounding tissue by thresholding followed by region growing. The model was meshed with tetrahedral elements and linear elastic material properties for bone were assigned to the model (Young's Modulus, E, of 17kGPa and a Poisson's ratio of 0.3). After boundary conditions were assigned, the bottom of the tibia was fixed in space and the top was compressed by 0.1 mm in axial direction. Stiffness was determined by recording the sum of the reaction forces of all elements and dividing it by the displacement (k=F/x). We observed increases in bone volume and in bone stiffness (14.8% +/- 2.6 and 29.6% +/- 5.0, respectively) due to row training.



FES rowing results in increased tibial bone volume and stiffness. Bone stiffness was plotted as a function of volume for four SCI subjects (●, ■, ▲ and ◆) after 6 months of row-training. Rowing increased stiffness and volume in all four subjects.



FES rowing improves tibial stress distribution. This image demonstrates the change in stress distribution in response to the same axial force (10 kN) at the tibia in the same subject before and after FES-row training. Stress values are normalized to 0 - 1 (0: blue, no stress to 1: red, max stress). The overall stiffness of the bone (i.e., its ability to withstand axial compression) was improved by almost 50%, from ~43 to ~64 kN/mm). This indicates improved bone strength and better stress distribution.

Reportable Outcomes

The following work was presented at national or international conferences in the past year. This work is directly related to the study aims:

Dr. Morse presented a poster at the 2012 Annual ISCoS meeting in London, England in September 2012 entitled *FES-rowing improves bone micro architecture and strength in the paralyzed lower extremity.*

Drs. Taylor presented an oral presentation at the American Spinal Injury Association annual meeting in Colorado (April 19-21, 2012): *Effect of a Regular Rowing Exercise Program on Maximal Exercise Capacity in Spinal Cord Injury (SCI) (Taylor, Morse).*

Conclusion

We have ended the second year of the study with great success in recruitment and testing. We continue to proceed with recruitment and anticipate reaching the study goals in the next 6 months. We are successfully row-training subjects and have administered zoledronic acid infusions without adverse events. Our research team is productive, efficient, and communicates well to complete study tasks. We have presented our preliminary findings at national and international conferences with good reception.

References

Not applicable.

Appendices

None.